AMENDMENTS TO THE SPECIFICATION

Please replace paragraph beginning on page 4, line 5 with the following rewritten paragraph:

FIG. 1 depict the construction of an oligonucleotide library. FIG. 1(A) The vector fAFF1 contains two non-complementary BstXI sites separated by a 30 bp stuffer fragment. Removal of the BstXI fragment allows oriented ligation of oligonucleotides with the appropriate cohesive ends (SEQ ID NOS:1-13). FIG. 1(B) The oligonucleotide ON-49 was annealed to two "half-site" fragments to form cohesive termini complementary to BstXI sites 1 and 2 in the vector. The gapped structure, where the single-stranded region comprises the variable hexacodon sequence and a 2 (gly) codon spacer, was ligated to the vector and electro-transformed into E. coli (SEQ ID NOS:14-17).

Please replace paragraph beginning on page 4, line 16 with the following rewritten paragraph:

FIG. 2 depicts the amino acid sequences (deduced from DNA sequence) of the N-terminal hexapeptides on pIII of infectious phage randomly chosen from the library. Sequences begin at the signal peptidase site. Single letter code for amino acids is A (Ala), C (Cys), D (Asp), E (Glu), F (Phe), G (Gly), H (His), I (Ile), K (Lys), L (Leu), M (Met), N (Asn), P (Pro), Q (Gln), R (Arg), S (Ser), T (Thr), V (Val), W (Trp), Y (Tyr) (SEQ ID NOS:18-69).

Please replace paragraph beginning on page 5, line 1 with the following rewritten paragraph:

FIG. 4 shows the amino acid sequences (deduced from DNA sequence) of the N-terminal peptides of. pIII of 52 phage isolated by three rounds of panning on mAB 3E7 (SEQ ID NOS:70-119).

Please replace paragraph beginning on page 17, line 32 with the following rewritten paragraph:

Construction of the cloning site at the 5'-region of gene III was accomplished by first removing a BstXI restriction site already present in the TN10 region of fdTet, RF DNA was digested with BstXI restriction endonuclease, and T4 DNA polymerase was added to remove the protruding 3' termini. Blunt-ended molecules were then ligated and transformed into MC1061 cells. RF DNA isolated from several tetracycline resistant transformants was digested again with BstXI; a clone that was not cleaved was selected for construction of the double BstXI site. Site-directed mutagenesis (Kunkel et al., Meth. Enzymol. 154:367-382 (1987), incorporated by reference herein) was carried out with the oligonucleotide

5'-TAT GAG GTT TTG CCA GAC AAC TGG AAC AGT TTC AGC GGA GTG CCA GTA GAA TGG AAC AAC TAA AGG (SEQ ID NO:120). Insertion of the correct mutagenic sequence was confirmed by dideoxy sequencing of RF DNA isolated from several tetracycline-resistant transformants.

Please replace paragraph beginning on page 18, line 19 with the following rewritten paragraph:

A collection of oligonucleotides encoding all possible hexapeptides was synthesized with the sequence 5'-C TCT CAC TCC (SEQ ID NO:14) $(NNK)_6$ GGC GGC ACT GTT GAAAGT TGT-3' (SEQ ID NO:15). N was A, C, G, and T (nominally equimolar), and K was G and T (nominally equimolar). This sequence, designated ON-49, was ligated into the BstXI sites of fAFF1 after annealing to two "half-site" oligonucleotides, ON-28 (5'-GGA GTG AGA GTA GA-3') (SEQ ID NO:121) and ON-29 (5'-CTT TCA ACA GT-3') (SEQ ID NO:122), which are complementary to the 5'- and 3'- portions of ON-49, respectively. "Half-site" oligonucleotides anneal to the 5'- and 3'- ends of oligonucleotide ON-49 to form appropriate BstXI cohesive ends. This left the appropriate BstXI site exposed without the need to digest with BstXI, thus avoiding the cutting of any BstXI sites that might have appeared in the variable region. The vector fAFF1 (100 μg) was digested to completion with BstXI, heat inactivated at 65.degree. C., and ethanol precipitated twice in the presence of 2M ammonium acetate. Oligonucleotides were phosphorylated with T4 kinase, and annealed in 20 mM Tris-HCl, pH 7.5, 2 mM MgCl.sub.2, 50 mM NaCl, by mixing 1.5 μg ON-28, 1.2 μg ON-29, and 0.5 μg ON-49 with 20 μg BstXI-digested fAFF1 RF DNA, heating to 65° C. for 5 minutes and allowing the mixture to cool slowly to room temperature. This represented an approximate molar ratio of 1:5:100:100 (fAFF1 vector: ON-49: ON-28: ON-29). The annealed structure is then ligated to BstXI-cut fAFF1 RF DNA to produce a double-stranded circular molecule with a small, single stranded gap. These molecules may be transformed into host cells. The annealed DNA was ligated in 20 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 2 mM DTT, 1 m MATP, by the addition of 20 units of T4 DNA ligase and incubated overnight at 15°C.

Please replace paragraph beginning on page 21, line 9 with the following rewritten paragraph:

After the final round of panning and amplification, a portion of the eluate was used to infect cells that were plated at low density on LB tetracycline plates. To analyze the diversity of peptide sequences in the library in a more direct way, we picked 52 individual colonies producing infectious phage, and sequenced the DNA of their variable regions. Individual colonies were picked and transferred to culture tubes containing 2 ml LB tetracycline and grown to saturation. Phage DNA was isolated by a method

designed for the Beckman Biomek Workstation employing 96-well microtiter plates (Mardis and Roe, Biotechniques 7:840-850 (1989), incorporated by reference herein). Single stranded DNA was sequenced using Sequenase 2.0 and an oligonucleotide sequencing primer (5'-CGA TCT AAA GTT TTG TCG TCT-3') (SEQ ID NO:123) which is complementary to the sequence located 40 nucleotides to the 3' side of the second BstXI site in fAFF1.

Please replace paragraph beginning on page 24, line 6 with the following rewritten paragraph:

Monoclonal antibody 3E7 binds to B-endorphin and, like the delta-opioid receptor, recognizes the N-terminal portion of the protein (Tyr-Gly-Gly-Phe) (SEQ ID NO:124), which is present on most natural opioid peptides. The antibody also binds tightly to leu- and met-enkephalin (YGGFL (SEQ ID NO:125), YGGFM (SEQ ID NO:126)), and a variety of related opioid peptides (Meo et al., Proc. Natl. Acad. Sci. USA 80:4084-4088 (1983), Herz et al., Life Sciences 31:1721-1724 (1982), and Gramsch et al., J. Neurochem. 40:1220-1226 (1983). The N-terminal hexapeptide library was screened against 3E7 by carrying out three rounds of panning, elution, and amplification. The recoveries of phage from this process are shown in Table 3. In each round the proportion of phage adsorbed to the antibody increased by about 100-fold, and in the last round, over 30% of the input phage were recovered. These results indicated that phage were preferentially enriched in each panning step.

Please replace paragraph beginning on page 27, line 15 with the following rewritten paragraph:

The previously reported high degree of specificity of the 3E7 antibody for the intact N-terminal epitope Tyr-Gly-Gly-Phe (SEQ ID NO:124) which is common to naturally occurring opioid peptides, Meo et al., supra, was verified. Removal of Tyr or deletion of any of the amino acids of the sequence Tyr-Gly-Gly-Phe-Leu (SEQ ID NO:125) had deleterious effect on binding affinity (Table 5).

Please replace paragraph beginning on page 27, line 21 with the following rewritten paragraph:

Shown in Table 5 are the IC50 for the six peptides which were identified by the phage panning method and chemically synthesized. Under the conditions of the radioimmunoassay (30 pM [^{125}I]b-endorphin; 20% tracer bound; 18 hr. incubation), the IC50 should be very close to the dissociation constant (Kd) for the peptide. The peptides are all relatively low affinity compared to YGGFL (SEQ ID NO:125), with IC50's ranging from 0.35 to 8.3 μM.

Please replace paragraph beginning on page 28, line 3 with the following rewritten paragraph:

TABLE 5: Relative affinities of peptides for 3E7 antibody determined by solution radioimmunoassay.[a]

Peptide	SEQ ID NO	N	IC50	(μM)	Affinity Relative to YGGFL
YGGFL	SEQ ID NO:125	(6)	0.0071	(0.0054,0.0093)	1
YGGF	SEQ ID NO:124	(3)	0.19	(0.093,0.38)	0.037
YGGL	SEQ ID NO:127	(3)	3.8	(2.1,6.6)	0.0018
YGFL	SEQ ID NO:128	(3)	28	(17,47)	0.00025
YGG		(2)	>1000		<0.0000071
GGFL	SEQ ID NO:129	(2)	>1000		<0.0000071
GGF		(2)	>1000		<0.0000071
GFL		(2)	>1000		<0.0000071
YGFWGM	SEQ ID NO:112	(3)	0.35	(0.19,0.63)	0.020
YGPFWS	SEQ ID NO:114	(3)	1.9	(1.3,2.8)	0.0037
YGGFPD	SEQ ID NO:83	(3)	2.3	(1.4,3.7)	0.0031
YGGWAG	SEQ ID NO:79	(3)	7.8	(6.0,10)	0.00091
YGNWTY	SEQ ID NO:104	(3)	7.8	(4.0,15)	0.00091
YAGFAQ	SEQ ID NO:118	(3)	8.3	(3.8,18)	0.00086

[a] = Data are geometric means and 95% confidence intervals (calculated from S.E.M. of log IC50) from the number (N) of independent determinations indicated.

Please replace paragraph beginning on page 28, line 39 with the following rewritten paragraph:

The panning procedure we have utilized employs extensive washing to remove non-specifically bound phage. Binding experiments with mAb 3E7 and [^{3}H]YGGFL (SEQ ID NO:125) indicate a rapid dissociation rate, approximately $t_{1/2}$=45 seconds at room temperature. Therefore, the ability to select phage bearing peptides with relatively low affinities may be the result of multivalent interaction between phage and antibody, as each phage typically has up to 4 or 5 copies of the pIII protein and each protein may carry a foreign peptide from the phage library.

Please insert the enclosed 24-page text entitled "SEQUENCE LISTING" immediately preceding the claims.